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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/801,669	03/17/2004	Wei-Wu He	PF140P1D2	4076

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HUMAN GENOME SCIENCES INC.
INTELLECTUAL PROPERTY DEPT.
14200 SHADY GROVE ROAD
ROCKVILLE, MD 20850

EXAMINER	
FOSTER, CHRISTINE E	
ART UNIT	**PAPER NUMBER**
1641	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/801,669	HE ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *3/17/04* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Please note that the Examiner in your application has changed. The new Examiner, Christine Foster, may be reached at 571-272-8786.

Election/Restrictions

1. Applicant's election with traverse of Group XV, claim 19, drawn to a diagnostic process in the reply filed on November 14, 2006 is acknowledged. The traversal is on the ground(s) that a search of all inventions would not present a serious search burden (Reply, p. 4-5). This is not found persuasive because the record as clearly set forth in the previous Office action reflects that Groups I-XVIII are patentably distinct and that a search of all inventions would represent a significant burden. Applicant's arguments that many if not most publications that disclose a protein also disclose nucleic acids encoding the protein, antibodies to the protein, and methods of making and using same are not persuasive, since separate searches of all of these independently would still be necessary in order to perform a thorough and complete search of the various inventions. For the reasons set forth in the previous Office action, the searches required to search the various inventions are largely non-coextensive and would therefore represent a serious search burden.

The requirement is still deemed proper and is therefore made FINAL.

2. Applicant's reply includes an amendment canceling all previously pending claims, and presenting new claims 21-35. The new claims 21-35 are subject to examination below.

Specification

3. The specification is objected to for the following reason:

The specification on page 1 should be amended to reflect the most current priority status of the present application, including proper reference to applications that have been issued or abandoned. Specifically, Applicant is requested to update the reference to Application No. 09/618,508 to reflect the issuance of the application as US 6,835,555.

Information Disclosure Statement

4. Applicant is reminded that the listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Specification

5. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant is requested to amend the title to reflect the elected invention of an assay method.

Claim Objections

6. Applicant is advised that should claim 28 be found allowable, claim 32 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 101

7. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. Claim 33 is rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

The claim recites the step of "using the result" of the immunoassay method "in a diagnostic method". However, the specification does not disclose any specific named diseases that could be diagnosed using the claimed immunoassay method. The specification at [0095] refers to a "diagnostic assay", but is silent with respect to what diseases might be diagnosed. This amounts to a recitation of an unspecified disease.

Applicant has not reasonably confirmed what disease or diseases could be diagnosed by the immunoassay method of the invention. The specification does not mention any specific diseases, and does not document altered levels of ICE-LAP 3 in connection with any specific named disease. Further research would be needed to first identify what diseases, if any, may be associated with altered levels of ICE-LAP 3.

9. Claim 33 is also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

The nature of the invention is directed to the identification of the ICE-LAP-3 protein. The specification discloses the full amino acid sequence for the putative mature from of this protein (SEQ ID NO:2), and outlines art-recognized methodology for producing antibodies against the protein [0104]-[0107], which could be used in assays to detect levels of ICE-LAP 3 [0095]-[0096].

Claim 33 relates to a diagnostic method "using the results" of such an assay method. The specification speculates that altered levels of ICE-LAP 3 may be detected in various tissues for use in a diagnostic assay [0095].

The courts have stated that "tossing out the mere germ of an idea does not constitute enabling disclosure." Genentech, 108 F.3d at 1366 (quoting Brenner v. Manson, 383 U.S. 519, 536 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion")). "[R]easonable detail must be provided in order to enable members of the public to understand and carry out the invention." Id.

In the instant case, such reasonable detail is lacking. The specification is entirely devoid of any teaching or data relating to detection of altered levels of ICE-LAP 3 in connection with disease. No specific diseases are mentioned that might be diagnosed by measuring altered levels

of ICE-LAP 3. *This amounts to a recitation of an unspecified disease*. The specification does not document any instances in which ICE-LAP 3 levels were observed to be altered in any disease. Applicant has not reasonably confirmed what disease or diseases, if any, could be diagnosed by the immunoassay method of the invention.

As a result, in order to carry out the claimed invention, further research would be needed to first identify what diseases might be associated with altered levels of ICE-LAP 3. One skilled in the art would need to conduct basic research to determine whether levels of ICE-LAP 3 were in fact altered in a specific disease by obtaining samples from subjects known to have a given disease, comparing the levels of ICE-LAP 3 in the samples to those obtained from healthy control subjects, and determining whether statistically significant changes were observed. In addition, one skilled in the art would also need to determine what levels or ranges of levels of ICE-LAP 3 would be indicative of disease. Such clinical investigative research to test and validate ICE-LAP 3 for use in diagnosis is not of a routine nature and clearly represents an undue burden.

For example, Bast et al. ("Translational Crossroads for Biomarkers" *Clin Cancer Res* 2005; 11(17), 6103-6108) point to the "lengthy process" of assay development and validation and note that many markers that correlate with disease statistically may not prove to be useful clinically (p. 6105, right column). See also LaBaer et al. ("So, You Want to Look for Biomarkers" *Journal of Proteome Research* 2005; 4, 1053-1059), which teaches that crucial validation steps are needed to demonstrate that an identified biomarker is a reliable predictor, and also that the process of converting such a biomarker into a practical clinical test is even more daunting (p. 1053, see the paragraph bridging the left and right columns). Baker ("In Biomarkers

We Trust?" *Nature Biotechnology* 2005; 23(3), 297-304) also speaks to the unpredictability involved in clinically applying biomarkers (see p. 298, the section "Walking on Thin Ice"):

"Using a new biomarker is like walking across a frozen lake without knowing how thick the ice is," says Ole Vesterqvist..."You start walking, and you get comfortable. Then you break through."

Thus, the state of the art teaches the unpredictability associated with the clinical use of biomarkers even after a biomarker has been correlated with a specific disease state.

The breadth of the claims is also clearly at issue, since claim 33 would encompass diagnosis of any disease. However, there are no working examples in which the claimed immunoassay method was used to diagnose any disease.

It is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling." In the instant case, the specification discloses that the ICE-LAP-3/SEQ ID NO:2 protein is a *newly identified* polypeptide (see especially [0002]).

One cannot extrapolate the teaching of the specification to the scope of the claims because said teachings represent insufficient guidance and objective evidence to predictably enable the use of the claimed invention.

In summary, due to the lack of direction/guidance presented in the specification regarding what diseases might be diagnosed using the claimed immunoassay method and how this would be accomplished, and in light of the state of the prior art, which fails to teach that altered levels of ICE-LAP-3 were known to be correlated with disease, as well as the unpredictability associated with validating biomarkers for clinical use, the lack of working examples showing use of the immunoassay methods of the invention for diagnostic purposes, and the breadth of the claims, the specification fails to teach the skilled artisan how to make and use the claimed invention without undue experimentation.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 21-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

12. New claim 21 (added via the preliminary amendment of November 14, 2006) recites "an antibody or fragment thereof that binds a polypeptide consisting of at least contiguous amino acid residues of SEQ ID NO:2" and further recites the step of "detecting binding of polypeptides from said sample to said antibody".

Applicant's reply does not indicate where support could be found in the specification for the newly presented claims. The new claims represent a departure from the specification and claims as originally filed for the following reasons.

The specification discloses SEQ ID NO:2, which is the putative mature form of the polypeptide ICE-LAP-3 lacking the N-terminal methionine residue (see for example at p. 3, [0019]). The specification also refers to diagnostic assays for detecting altered levels of the ICE-LAP-3 protein (p. 19-20, paragraphs [0095]-[0096]).

The disclosure of assays to detect the single *species* of ICE-LAP-3 (SEQ ID NO:2) using antibodies specific to same does not fully support the instantly claimed invention, which relates not only to detection of the single protein ICE-LAP-3 (SEQ ID NO:2), but to the detection of a *genus* of polypeptides that would be bound by antibodies that bind to polypeptides "consisting of at least 30 contiguous amino acid residues of SEQ ID NO:2". There is no disclosure of assays to detect this genus of polypeptides. In disclosing only assays to detect full-length ICE-LAP-3 (SEQ ID NO:2) using antibodies specific to same, the specification does not provide a written description of the currently claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed. The MPEP lists factors that can be used to determine if sufficient evidence of

possession has been furnished in the disclosure of the application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention." MPEP 2163.

It is known that antibodies recognize relatively small regions, termed epitopes, on antigen. See Harlow & Lane (Harlow, E. and Lane, D., Antibodies: A Laboratory Manual (1988) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, pages 23-26, especially at p. 23-24). Because antibodies can recognize relatively small regions of antigens, they can cross-react with similar epitopes on related molecules. However, the presence of similar epitopes does not necessarily imply a functional relationship. See Harlow & Lane at p. 24.

As such, "an antibody or fragment thereof that binds a polypeptide consisting of at least 30 contiguous amino acid residues of SEQ ID NO:2" would likely contact only a small region on the at least 30 contiguous residues of SEQ ID NO:2. As a result, the genus of polypeptides that are detected by the claimed method in step (b) are not limited to those polypeptides that have at least 30 contiguous amino acids. Rather, any cross-reacting polypeptide having a similar epitope would be bound by the antibody and detected.

However, the specification does not support the detection of the genus of such cross-reacting polypeptides claimed because Applicant has described only SEQ ID NO:2. The specification does not identify any examples of epitopes that would be shared among the polypeptides detected. One skilled in the art would not envisage possession of methods of detecting the genus of polypeptides capable of binding to antibodies that bind to polypeptides

"consisting of at least 30 contiguous amino acid residues of SEQ ID NO:2" because such a genus has not been adequately described.

Applicant has described the genus of polypeptides to be detected only by reference to a functional characteristic, namely, the ability be bound by antibodies that bind to polypeptides "consisting of at least 30 contiguous amino acid residues of SEQ ID NO:2". Although presumably this genus of polypeptides to be detected shares a similar antibody epitope in common, Applicant has not described any examples of such epitopes that would be shared by the members of the genus. As such, the common structure shared by the genus of polypeptides to be detected is not known. Applicant has not disclosed any partial structure that would be correlated with function (i.e., ability to bind to the antibodies).

Applicant has also not identified what portions of SEQ ID NO:2 would be likely to be antigenic, i.e., what portions or amino acid sequences define antibody epitopes.

Harlow & Lane further teach that antibody epitopes can be formed by contiguous, as well as by noncontiguous amino acid sequences (p. 25). In the latter case, amino acids far apart in the protein's primary sequence can come together in space in the three-dimensional structure of the folded protein to form conformational epitopes. However, Applicant has not described the three-dimensional structure of the folded SEQ ID NO:2 protein, and has not identified any examples of such conformational epitopes. One skilled in the art cannot envisage possession of detection of polypeptides that share a similar *conformational* epitope in common since no such epitopes are described, and because the conformation or three-dimensional structure of the SEQ ID NO:2 protein is also not described.

In summary, because the specification does not describe any specific epitopes that would be recognized by antibodies, Applicant has failed to describe any common structure that would be shared among members of the genus of polypeptides to be detected. One skilled in the art would not envisage possession of methods of detecting the genus of polypeptides capable of binding to antibodies that bind to polypeptides "consisting of at least 30 contiguous amino acid residues of SEQ ID NO:2" because such a genus has not been adequately described.

The claimed invention also represents new matter because Applicant has not described any antibodies or fragments thereof that bind "a polypeptide consisting of at least 30 contiguous amino acid residues of SEQ ID NO:2". Although the specification mentions polypeptides that *contain* at least 30 amino acids of SEQ ID NO:2 [0043], there is no disclosure of antibodies that bind to such polypeptides, but only of antibodies that are specific to ICE-LAP 3 (the full-length SEQ ID NO:2).

Applicant has also not established that antibodies that bind to ICE-LAP 3/SEQ ID NO:2 would inherently bind to polypeptides consisting of at least 30 contiguous amino acids of SEQ ID NO:2. As taught in Harlow & Lane above, antibody epitopes may be formed by amino acids far apart in the primary sequence, such that an antibody that binds to the full-length protein may not recognize a fragment.

It is also noted that the disclosure of polypeptides *containing* at least 30 amino acids of SEQ ID NO:2 differs in scope from the instantly recited polypeptides *consisting of* at least 30 amino acids of SEQ ID NO:2.

Applicant has also not described any *specific* antibodies or fragments thereof that could be used in the claimed detection method, but only mentions antibodies raised against SEQ ID

NO:2. No antibodies or fragments thereof are described with any particularity in the specification. No partial structure of the antibodies useful according to the present invention is disclosed. No correlation is disclosed between any such partial structure and function (binding to the claimed polypeptides).

Because neither the common epitope(s) on the polypeptides to be detected, nor the specifics of the antibodies themselves are adequately described in the specification, one skilled in the art cannot envisage possession of the claimed detection methods. Applicant is attempting to describe an unknown by reference to another unknown.

In summary, the specification discloses only detection of ICE-LAP 3 (full-length SEQ ID NO:2) using antibodies specific to same, and does not disclose methods of detecting a genus of polypeptides that bind to antibodies capable of recognizing polypeptides that consist of at least 30 contiguous amino acids of SEQ ID NO:2. Although Applicant has described detection of SEQ ID NO:2 using antibodies that bind to SEQ ID NO:2, the disclosure does not support the claimed methods of detecting "polypeptides" that are bound by antibodies that bind polypeptides "consisting of at least 30 contiguous amino acids" since neither the specific sequence(s) or epitope(s) that would be recognized by such an antibody, nor the specific antibodies themselves, are adequately described in the specification.

13. New claim 23 recites an immunoassay method "wherein said antibody or fragment thereof is bound to a solid support".

The specification mentions at [0096] that *competition assays* may be employed wherein antibodies specific to ICE-LAP 3 are attached to a solid support. However, the specification does

not describe other methods in which antibodies are coupled to a solid support. There is no generic disclosure of immunoassay methods wherein antibodies or fragments thereof are bound to a solid support. The introduction into the claims of the limitation that the antibody or fragment thereof is bound to a solid support, without the accompanying limitation of a competition assay involving labeled ICE-LAP, changes the scope of the disclosure as-filed and therefore represents new matter.

14. New claim 24 recites that the detecting step "comprises generating a signal from a reporter antibody to which a detectable reagent is attached".

The specification mentions at [0096] that in an ELISA assay, a reporter antibody is prepared against a monoclonal antibody specific to ICE-LAP 3. Such reporter antibodies may be attached to detectable reagents. The incorporation into the claims the limitation of a reporter antibody, without the accompanying limitations that the reporter antibody is specific to a monoclonal anti-ICE-LAP 3 antibody for use in an ELISA assay, changes the scope of the disclosure as-filed and therefore represents new matter. The genus of reporter antibodies claimed is not fully supported by the disclosed species of reporter antibodies that are secondary antibodies, and would encompass, for example, reporter antibodies that are specific for second epitopes on ICE-LAP 3 (as in a sandwich or two-site immunoassay). The specification does not describe such reporter antibodies.

15. New claim 29 recites that the antibody is a "human" antibody. Support could not be found in the specification for such antibodies, or for their use in the claimed immunoassay

methods. The specification at [0104], [0107] mentions *humanized* antibodies, but not human antibodies. Rather, the specification discloses at [0105] that the antibodies of the present invention are preferably obtained by immunizing a *nonhuman* animal.

16. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

17. Claim 34 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

18. Claim 34 recites the limitation "said tissue sample" in line 3. There is insufficient antecedent basis for this limitation in the claim.

Double Patenting

19. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

20. Claims 21-22 and 26-32 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-61 of U.S. Patent No. 6,733,981 B2.

21. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '981 patent also claims an immunoassay method (such as an ELISA) in which a biological sample is contacted with an isolated antibody or fragment thereof that binds a polypeptide consisting of at least 30 contiguous amino acid residues of SEQ ID NO:2, followed by detection of bound protein (see especially claims 17-18 and 42-44).

Specifically, the '981 patent claims methods of detecting ICE-LAP 3 (SEQ ID NO:2) using antibodies that specifically bind to polypeptides consisting of amino acid residues 1-303 or 2-303 of SEQ ID NO:2, which represent species that anticipates the genus of "at least 30 contiguous amino acid residues of SEQ ID NO:2" as claimed in instant claim 21. Further, the detection of ICE-LAP 3 in the '981 patent represents a species that anticipates the genus of "polypeptides" that are detected in the instantly claimed immunoassay method.

With respect to instant claims 26-32, the antibodies of the '981 patent may be monoclonal (see claim 10), chimeric, humanized, single chain, or a Fab fragment (see claim 11).

22. Claims 23-25 and 34 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-61 of U.S. Patent No. 6,733,981 B2 in view of Harlow & Lane (Harlow, E. and Lane, D., Antibodies: A Laboratory Manual (1988) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, pages 321-323, 584-585, and 591-592).

The '981 patent is as discussed above, which teaches an immunoassay method to detect ICE-LAP 3 (SEQ ID NO:2) using an antibody that binds a polypeptide consisting of at least 30 contiguous amino acid residues of SEQ ID NO:2 by contacting the antibody with a biological sample and detecting binding of ICE-LAP 3 (see especially claims 1 and 17-18).

The '981 patent differs from the claimed invention in that it fails to specifically teach that binding is detected by generating a signal from a reporter antibody to which a detectable reagent is attached. The '981 patent also fails to specifically teach that the antibody is bound to a solid support.

Harlow & Lane teach that all immunoassays rely on labeled reagents for detection (p. 591-592), and that detection may be direct or indirect (p. 321-323). In indirect detection methods, the antigen-specific antibody is unlabeled and need not be purified. Its binding to the antigen is detected by a secondary reagent, such as labeled anti-immunoglobulin antibodies or labeled protein A (ibid). Indirect methods are the most useful for the majority of applications and offer the advantages of widely available labeled reagents, such that the same reagents can be used to detect a large range of antigens and are available commercially. Also, the primary antibody is not modified so the loss of activity is avoided. See p. 321. Such secondary or reporter reagents can be labeled with detectable reagents such as radioactive iodine, enzyme or fluorochrome labels (see p. 322 and 591-592).

Therefore, with respect to claims 24-25, it would have been obvious to one of ordinary skill in the art to employ a secondary or reporter reagent labeled with an enzyme or fluorochrome label as taught by Harlow & Lane in the method of detecting ICE-LAP 3 of the '981 patent. One would be motivated to do this because Harlow & Lane teach that such indirect methods avoid

potential loss of activity associated with directly labeling the antigen-specific antibody, and also have the advantage that the same secondary or reporter antibodies are commercially available and can be used for detecting a large range of antigens.

Harlow & Lane further teach antigen capture immunoassays for detection of antigens, in which an antibody is bound to a solid phase and used to capture antigen in the sample, which is subsequently quantitated (see especially p. 584-585). This immunoassay format has the advantage of being rapid, easy, and quantitative. Harlow & Lane further teach that to quantitate the levels of antigen in the sample according to this assay format, a standard or titration curve can be used (p. 585).

Therefore, with respect to claims 23 and 34, it would have been obvious to one of ordinary skill in the art to employ the antigen capture immunoassay format of Harlow & Lane (in which the antigen-specific antibody is bound to a solid support) in order to perform the immunoassay method of detecting ICE-LAP 3 of the '981 patent. One would be motivated to do this because Harlow & Lane teach that antigen capture is a well-known immunoassay format that has the advantages of being rapid, easy, and quantitative. It would have been further obvious to employ a standard curve as taught by Harlow & Lane when using this assay format in order to quantitate the amount of ICE-LAP 3 in the sample.

23. Claim 35 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-61 of U.S. Patent No. 6,733,981 B2 in view of Fernandes-Alnemri et al. ("Mch3, a Novel Human Apoptotic Cysteine Protease Highly Related to CPP32" *Cancer Research* 55 (1995), 6045-6052) and in light of iHOP (Information Hyperlinked over

Proteins, entry for CASP7, downloaded from http://www.ihop-net.org/UniPub/iHOP/gs/86932.html on 2/13/2007).

The '981 patent is as discussed above, which teaches detection of the ICE-LAP 3 polypeptide in a biological sample using an antibody meeting the binding characteristics as recited in instant claim 21. However, the reference fails to specifically teach that the biological sample is a tissue sample obtained from a patient.

Fernandes-Alnemri teach the tissue distribution of Mch3 (see the entire document, especially the abstract and p. 6047-6048, especially Figure 4). The reference further teaches that

IHOP is relied upon as an evidentiary reference teaching that Mch3 as taught by Fernandes-Alnemri et al. is another name for the ICE-LAP 3 protein that is taught in the '981 patent. See top right, "Synonyms".

Therefore, it would have been obvious to employ the method of '981 in order to detect ICE-LAP 3 in a biological sample that is a tissue sample because Fernandes-Alnemri et al. teach that this protein is expressed in a number of tissues; it would have been obvious to select a type of biological sample in which the protein was known to be present in order to quantify the amount of protein in that sample.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 8:30-5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached at (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Christine Foster, Ph.D.
Patent Examiner
Art Unit 1641

LONG V. LE 02/16/07
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600